The Hashemite University
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Quality control and regulatory affairs
Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances

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The objective of the Q6A

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- This guideline is intended to assist in the establishment of a **single set** of **global specifications** for new drug substances and new drug products.
- It provides guidance on the **setting** and justification of **acceptance criteria** and the **selection of test procedures** for new drug substances of synthetic chemical origin, and new drug products produced from them, which have not been registered previously in the United States, the European Union, or Japan.
- **Acceptance criteria** means **numerical limits**, **ranges**, or **other criteria** for tests that are used for or in making a decision to accept or reject a unit, lot, or batch of a drug product.
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Specification

- A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described.
- It establishes **the set of criteria** to which a drug substance or drug product should conform to be considered **acceptable** for its **intended use** → Conformance to specification.
- Specifications are **critical quality** standards that are **proposed** and **justified** by the manufacturer and **approved** by regulatory authorities as conditions of approval.
- Specifications are one part of a total control strategy for the drug substance and drug product designed **to ensure product quality and consistency.**
- Specifications is an important component of **quality assurance.**

Scope of the guidelines

- The **quality** of drug and drug product is determined by:
  1. Design
  2. Development
  3. In-process control
  4. GMP control
  5. Process validation
  6. Specification
- ICH Q6A addresses specifications (tests, procedures, and acceptance criteria) which play a major role in assuring the quality of the **new drug substance** and **new drug product at release** and during **shelf life**.
- Guidance is provided with regard to acceptance criteria which should be established for all new drug substances and new drug products, i.e. **universal acceptance criteria**, and those that are considered specific to **individual drug substances and / or dosage forms**.

- Dosage forms included in this guideline are oral, liquid, and parenteral dosage forms (these are **models** for other dosage forms that have not been discussed in this guideline).

General concepts

- **Periodic or skip testing**

General concepts

- **Periodic or skip testing**
- Performance of specified tests at release on pre-selected batches and / or at predetermined intervals **(not batch to batch)**
- This represents a less than full schedule of testing and should therefore be justified and presented to and approved by the regulatory authority prior to implementation. (at minimum every 10 the batch, at least one batch annually).
- Examples:
  - Residual solvents and microorganism testing for solid oral DF.
- Only limited data may be available at the time of submission of an application **(generally implemented post-approval)**.
- Any failure to meet acceptance criteria established for the periodic test should be handled by proper notification of the appropriate regulatory authority.
- If these data demonstrate a need to restore routine testing, **then batch by batch release testing should be reinstated.**

General concepts

- **Release Vs. Shelf-life**
- Applicable **only** to drug product.
- The regulatory acceptance criteria are the same from release throughout shelf-life.
- The Release criteria are tighter to ensure to provide increased assurance to the applicant that the product will remain within the regulatory acceptance criterion throughout its shelf-life.

General concepts

- **In-process tests**
- Tests which may be performed during the manufacture of either the drug substance or drug product, rather than as part of the formal battery of tests which are conducted prior to release.
- In-process tests which are only used for the purpose of adjusting process parameters within an operating range.
- Certain tests conducted during the manufacturing process, where the acceptance criterion is identical to or tighter than the release requirement, (e.g., pH of a solution) may be **sufficient** to satisfy specification requirements when the test is included in the specification.
  - This approach should be validated to show that test results or product performance characteristics **do not change from the in-process stage to finished product**

General concepts

Design and development consideration

- The basis of specification are the experience and data accumulated during development of a new drug product.
- It is possible to exclude or replace tests based on the collecting data.

Examples:

- Particle size testing may fall into this category, may be performed as an in-process test, or may be performed as a release test, depending on its relevance to product performance.
- dissolution testing for immediate release solid oral drug products made from highly water soluble drug substances may be replaced by disintegration testing, if these products have been demonstrated during development to have consistently rapid drug release characteristics

General concepts

General concepts

Limited data available at filing

- **limited** amount of data may be available at the time of filing can influence the process **of setting acceptance criteria.**
- it may be necessary to propose revised acceptance criteria as additional experience is gained with the manufacture of a particular drug substance or drug product (example: acceptance limits for a specific **impurity**).
- The basis for the acceptance criteria at the time of filing should necessarily focus on **safety and efficacy.**
- When only limited data are available, the **initially approved tests** and acceptance criteria should **be reviewed as more information** is collected, with a view towards possible modification. This could involve **loosening**, as well as **tightening**, acceptance criteria as appropriate.

General concepts

Other test

Parametric release → usually at release →

- Can be used as an operational alternative to routine release testing for the drug product in certain cases when approved by the regulatory authority.
- Example:
  - Sterility testing for terminally sterilized drug products.
  - In this case, the release of each batch is based on satisfactory results from monitoring specific parameters, e.g., temperature, pressure, and time during the terminal sterilization phase(s) of drug product manufacturing.
  - **These parameters** can generally be **more accurately controlled and measured**, so that they are more reliable **in predicting sterility assurance** than is end-product sterility testing.
- Appropriate laboratory tests (e.g., chemical or physical indicator) may be included in the parametric release program.

General concepts

General concepts

Parametric release

- Alternative procedures are those which may be used to measure an attribute when such procedures control the quality of the drug substance or drug product to an extent that is **comparable or superior to the official procedure.**
- Example:
- For tablets that have been shown not to degrade during manufacture, it may be permissible to use a spectrophotometric procedure for release as opposed to the official procedure, which is chromatographic. However, the chromatographic procedure should still be used to demonstrate compiiance with the acceptance criteria during the shelf-life of the product

General concepts

Pharmacopoeial tests and acceptance criteria

- References to certain procedures are found in pharmacopoeias in each region. Wherever they are appropriate, pharmacopoeial procedures should be utilized.
- Whereas differences in pharmacopoeial procedures and/or acceptance criteria have existed among the regions, a harmonized specification is possible only if the procedures and acceptance criteria defined are acceptable to regulatory authorities in all regions.
- The Pharmacopoeial Discussion Group (PDG) of the European Pharmacopoeia, the Japanese Pharmacopoeia, and the United States Pharmacopeia has expressed a commitment to achieving harmonization of the procedures in a timely fashion.
  - the procedures and acceptance criteria from all three pharmacopoeias are considered equivalent and are, therefore, interchangeable.
  - no pharmacopoeia shall revise unilaterally any monograph or chapter after sign-off or after publication

General concepts

General concepts

Evolving technologies

New analytical technologies, and modifications to existing technology, are continually being developed. Such technologies should be used when they are considered to offer additional assurance of quality, or are otherwise justified.

General concepts

لازم مكون حندد

- It should not be necessary to test the drug product for quality attributes uniquely associated with the drug substance.
- Example:
  - it is normally not considered necessary to test the drug product for synthesis impurities which are controlled in the drug substance and are not degradation products.

(15)

some time عندي paracetamol drug وانا عاملة كل ال test المطلوبة عات ال assay

عات ال impurites عات كل شي مطلوب مني حتى اتأكد من ال quality

لا paracetamol وهاد بدي احطه مع exipent حتى يعطيني paracetamol product

مهمة جدا

drug substance → drug product

هون انا عاملة كل ال test ومتأكدة انه ال

exipent اللي رح اضيفها ما رح تأثر على ال quality

لل paracetamol ما بتأثر على ال assay ولا purity ولا

microorganism ولا اي شي فانا بس بكون عاملة و لازم

احلل quality test للشي ال (بشرط) احط ما يتأثر مع ال

drug substance ← qualify لكل all quality test وما رح اعيد ال

ال justify بحيث يكون اثر ال exipent ما أثر على ال product

General concepts

General concepts

Reference standard

- A reference standard, or reference material, is a substance prepared for use as the standard in an assay, identification, or purity test.
- It should have a quality appropriate to its use. It is often characterized and evaluated for its intended purpose by additional procedures other than those used in routine testing.
- For new drug substance reference standards intended for use in assays, the impurities should be adequately identified and / or controlled, and purity should be measured by a quantitative procedure.

Guidelines

- The applicant should specify which tests are routinely conducted batch-by-batch, and which tests are not, with an indication and justification of the actual testing frequency.
- The drug substance and / or drug product should meet the acceptance criteria if tested.
- Changes in the specification after approval of the application may need prior approval by the regulatory authority.

Guidelines

Justification of specifications

- When a specification is first proposed, **justification** should be presented for **each procedure and each acceptance criterion** included.
- The justification should refer to relèvant development data, pharmacopoeial standards, test data for drug substances and drug products used in toxicology and clinical studies, and results from accelerated and long term stability studies, as appropriate.
- A **reasonable range of expected analytical** and manufacturing variability should be considered.
- The applicant should justify **alternative approaches**
- Justification should **be based on data derived from the new drug** substance synthesis and/or the new drug product manufacturing process.
- Justification may consider **theoretical tolerances** for a given procedure or acceptance criterion, but the actual results obtained should form the primary basis for whatever approach is taken.

Guidelines

- Test results from stability and scale-up / validation batches, with emphasis on the primary stability batches, should be considered in setting and justifying specifications.
- If multiple manufacturing sites are planned, it may be valuable to consider data from these sites in establishing the initial tests and acceptance criteria.
- Justification for proposing exclusion of a test from the specification should be based on development data and on process validation data (where appropriate)

- **Content of the guidelines:**

  – **Universal tests/criteria**

  – **Specific tests/criteria**

Guidelines

- **Universal tests/criteria**
- Implementation of the recommendations on the criteria should take into account the ICH Guidelines Text on **Validation** of Analytical Procedures and Validation of Analytical Procedures: Methodology

- New drug substances → pure chemical supstance
- New drug products → product (active + exipent)

Universal tests/criteria
New drug substances

- **Description:** →
  - Qualitative statement
  - State (e.g. solid, liquid)
  - Color of the new drug substance.
  - If any of these characteristics change during storage, this change should be investigated and appropriate action taken.
- **Identification**
  - Identification testing should optimally be able to discriminate between compounds of closely related structure which are likely to be present.
  - Identification tests should be specific for the new drug substance, e.g., infrared spectroscopy.
  - New drug substances which are optically active may also need specific identification testing or performance of a chiral assay.

Universal tests/criteria
New drug substances

Assay

- A specific, stability-indicating procedure should be included to determine the content of the new drug substance.
- In many cases it is possible to employ the same procedure (e.g., HPLC) for both assay of the new drug substance and quantitation of impurities.
- In cases where use of a non-specific assay is justified, other supporting analytical procedures should be used to achieve overall specificity.

Universal tests/criteria
New drug substances

Universal tests/criteria
New drug substances

- **Impurities**
- Organic and inorganic impurities and residual solvents are included in this category.
- The threshold of impurities is defined.
- Decision tree #1 addresses the extrapolation of meaningful limits on impurities from the body of data generated during development.

New drug products

Description:

- A **qualitative** description of the dosage form should be provided (e.g., size, shape, and color).
- If any of these characteristics **change** during manufacture or storage, this change should be investigated and appropriate action taken.
- The acceptance criteria should include the final acceptable appearance. If color changes during storage, a **quantitative** procedure may be appropriate.

Universal tests/criteria
New drug products

Universal tests/criteria
New drug products

Identification

- Identification testing should establish the identity of the new drug substance(s) in the new drug product and should be able to discriminate between compounds of closely related structure which are likely to be present.
- Identity tests should be specific for the new drug substance, e.g., infrared spectroscopy.
- Identification solely by a single chromatographic retention time, for example, is not regarded as being specific. However, the use of two chromatographic procedures, where the separation is based on different principles, or combination of tests into a single procedure, such as HPLC/UV diode array, HPLC/MS, or GC/MS, is generally acceptable

Universal tests/criteria
New drug products

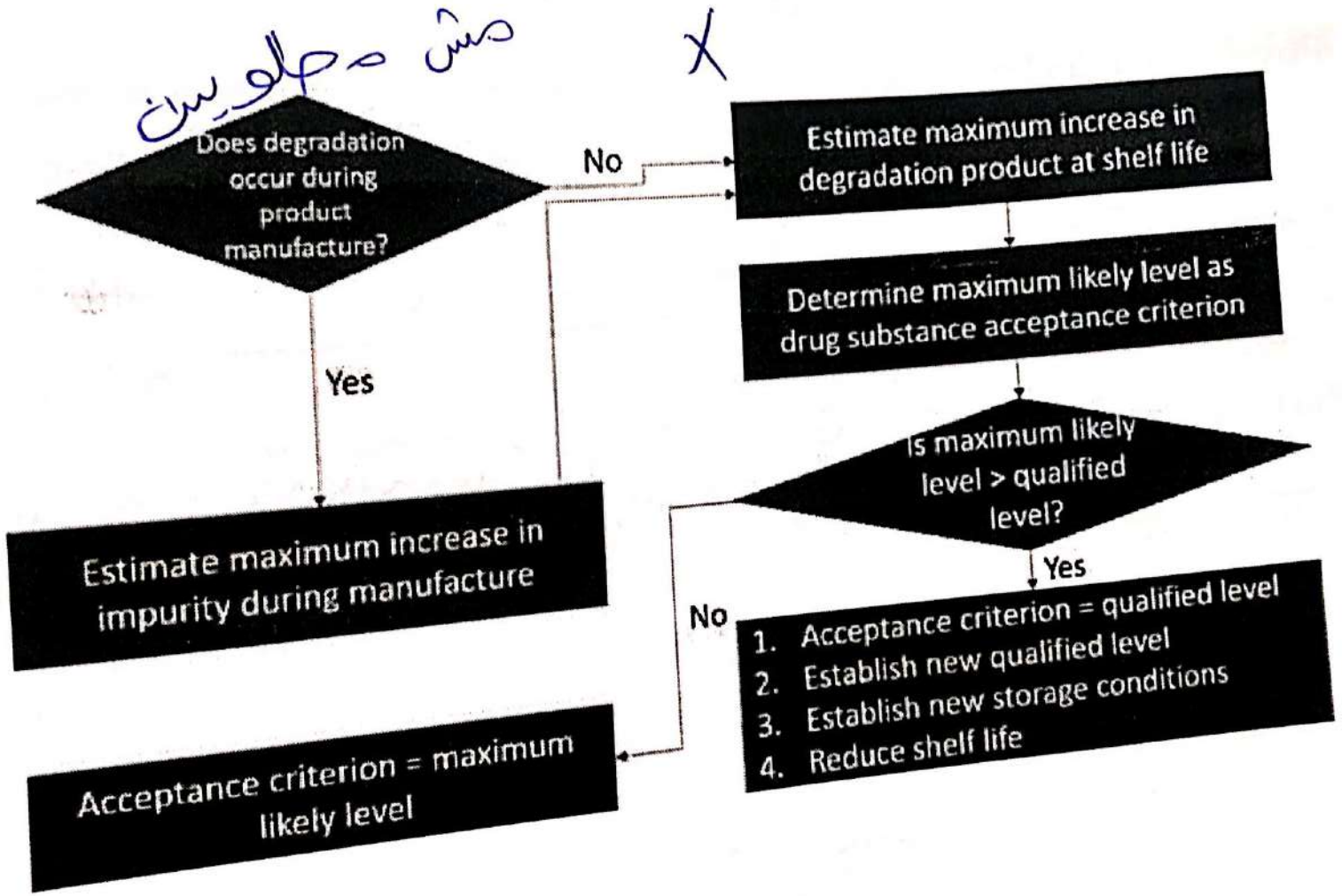
- **Assay**:
- A specific, stability-indicating assay to determine strength (content) should be
- included for all new drug products.
- In many cases it is possible to employ the same procedure (e.g., HPLC) for both assay of the new drug substance and quantitation of impurities.
- Results of content uniformity testing for new drug products can be used for quantitation of drug product strength, if the methods used for content uniformity are also appropriate as assays.
- In cases where use of a non-specific assay is justified, other supporting analytical procedures should be used to achieve overall specificity. For example, where titration is adopted to assay the drug substance for release, the combination of the assay and a suitable test for impurities can be used.
- A specific procedure should be used when there is evidence of excipient interference with the non-specific assay.

Universal tests/criteria
New drug products

Universal tests/criteria
New drug products

Impurities

- Organic and inorganic impurities (degradation products) and residual solvents are included in this category.
- Organic impurities arising from degradation of the new drug substance and impurities that arise during the manufacturing process for the drug product should be monitored in the new drug product.
- Acceptance limits should be stated for individual specified degradation products, which may include both identified and unidentified degradation products as appropriate, and total degradation products.
- Process impurities from the new drug substance synthesis are normally controlled during drug substance testing, and therefore are not included in the total impurities limit.
- When it has been conclusively demonstrated via appropriate analytical methodology, that the drug substance does not degrade in the specific formulation, and under the specific storage conditions proposed in the new drug application, **degradation product testing** may be reduced or eliminated upon approval by the regulatory authorities.
- Decision tree #2 addresses the extrapolation of meaningful limits on degradation products from the body of data generated during development.



Guidelines

Specific tests/criteria

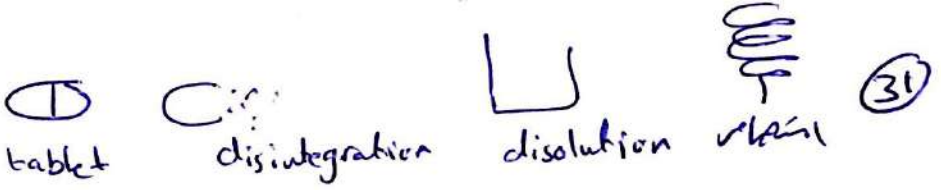
- **Specific tests** may be considered on a case by case basis for drug substances and/or drug products.
- Individual tests/criteria should be included in the specification when the tests have an impact on the quality of the drug substance and drug product for batch control.
- New drug substance
- New drug products

Specific tests/criteria
New drug substance

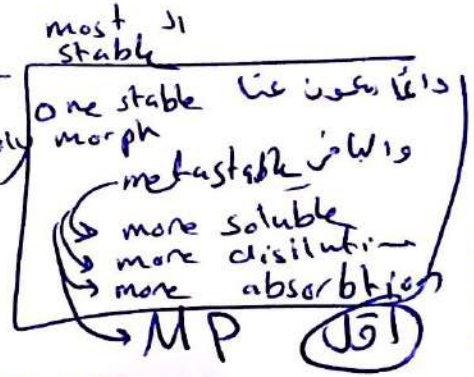
- **Physicochemical properties**
  - These are properties such as pH of an aqueous solution, melting point / range, and refractive index.
  - The procedures used for the measurement of these properties are usually unique and do not need much elaboration, e.g., capillary melting point, Abbé refractometry.
  - The tests performed in this category should be determined by the physical nature of the new drug substance and by its intended use.
- **Particle size**
  - Particle size can have a significant effect on dissolution rates, bioavailability, and / or stability.
  - Testing for particle size distribution should be carried out using an appropriate procedure, and acceptance criteria should be provided.
  - Decision tree #3 provides additional guidance on when particle size testing should be considered.

Specific tests/criteria
New drug substance

should be considered.



Specific tests/criteria
New drug substance



• Polymorphic forms

- Some new drug substances exist in different crystalline forms which differ in their physical properties.
- Polymorphism may also include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms.
- Differences in these forms could affect the quality or performance of the new drug products.

In cases where differences exist which have been shown to affect drug product performance, bioavailability or stability, then the appropriate solid state should be specified.

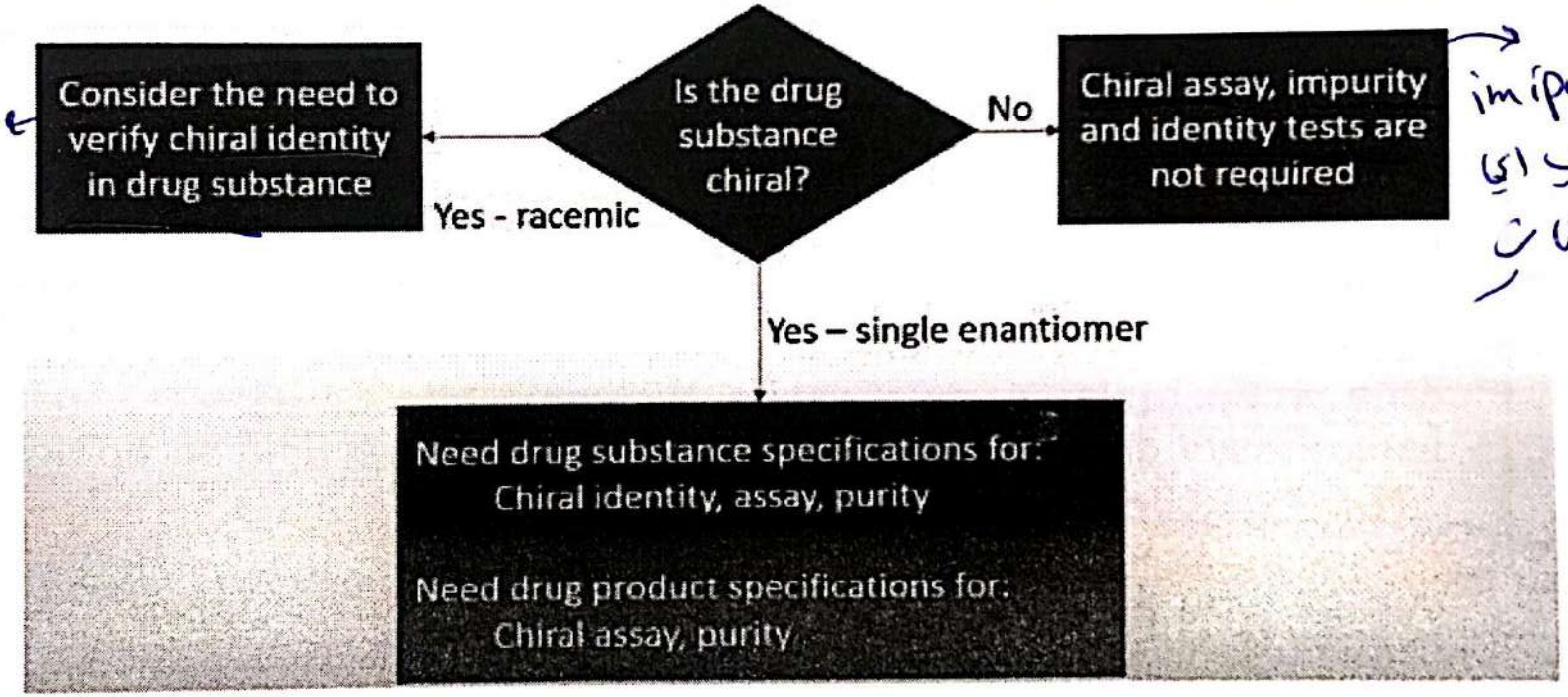
Physicochemical measurements and techniques are commonly used to determine whether multiple forms exist.

- Examples of these procedures are: melting point (including hot-stage microscopy), solid state IR, X-ray powder diffraction, thermal analysis procedures (like DSC, TGA and DTA), Raman spectroscopy, optical microscopy, and solid state NMR.

Specific tests/criteria
New drug substance

Tests for chiral new drug substances

- Where a new drug substance is predominantly one enantiomer, the opposite enantiomer is excluded from the qualification and identification thresholds given in the *ICH Guidelines on Impurities in New Drug Substances and Impurities in New Drug Products* because of practical difficulties in quantifying it at those levels.
- impurity in the chiral new drug substance and the resulting new drug product(s) should otherwise be treated according to the principles established in those Guidelines.
- Decision tree #5 summarizes when and if chiral identity tests, impurity tests, and assays may be needed for both new drug substances and new drug products, according to the following concepts:



Specific tests/criteria

New drug substance

Drug substance

- Impurities. For chiral drug substances which are developed as a single enantiomer, control of the other enantiomer should be considered in the same manner as for other impurities. Assurance of control also could be given by appropriate testing of a starting material or intermediate, with suitable justification.
- Assay. An enantioselective determination of the drug substance should be part of the specification. It is considered acceptable for this to be achieved either through use of a chiral assay procedure or by the combination of an achiral assay together with appropriate methods of controlling the enantiomeric impurity.
- Identity. For a drug substance developed as a single enantiomer, the identity test(s) should be capable of distinguishing both enantiomers and the racemic mixture.

Drug Product

- **Degradation products.** Control of the other enantiomer in a drug product is considered necessary unless racemization has been shown to be insignificant during manufacture of the dosage form, and on storage.
- **Assay:** An achiral assay may be sufficient where racemization has been shown to be insignificant during manufacture of the dosage form, and on storage.
- **Identity:** A stereospecific identity test is not generally needed in the drug product release specification. When racemization is insignificant during manufacture of the dosage form, and on storage.
- Stereospecific identity testing is **more appropriately addressed** as part of the drug substance specification. When racemization in the dosage form is a concern, chiral assay or enantiomeric impurity testing of the drug product will serve to verify identity.

Specific tests/criteria
New drug substance

Water content

- This test is important in cases where the new drug substance is known to be hygroscopic or degraded by moisture or when the drug substance is known to be a stoichiometric hydrate.
- The acceptance criteria may be justified with data on the effects of hydration or moisture absorption. In some cases, a Loss on Drying procedure may be considered adequate; however, a detection procedure that is specific for water (e.g., **Karl Fischer titration**) is preferred.

Inorganic impurities

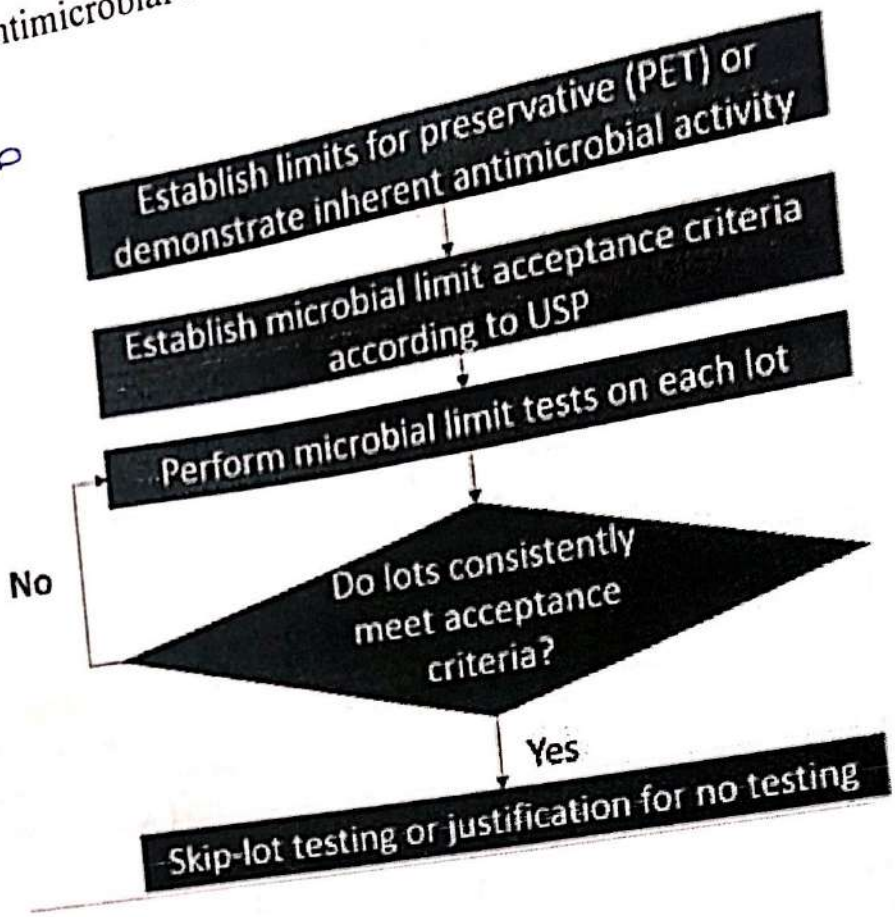
- The need for inclusion of tests and acceptance criteria for inorganic impurities (e.g., catalysts) should be studied during development and based on knowledge of the manufacturing process.
- Procedures and acceptance criteria for sulfated ash / residue on ignition should follow pharmacopoeial precedents.
- Other inorganic impurities may be determined by other appropriate procedures, e.g., atomic absorption spectroscopy.

Specific tests/criteria

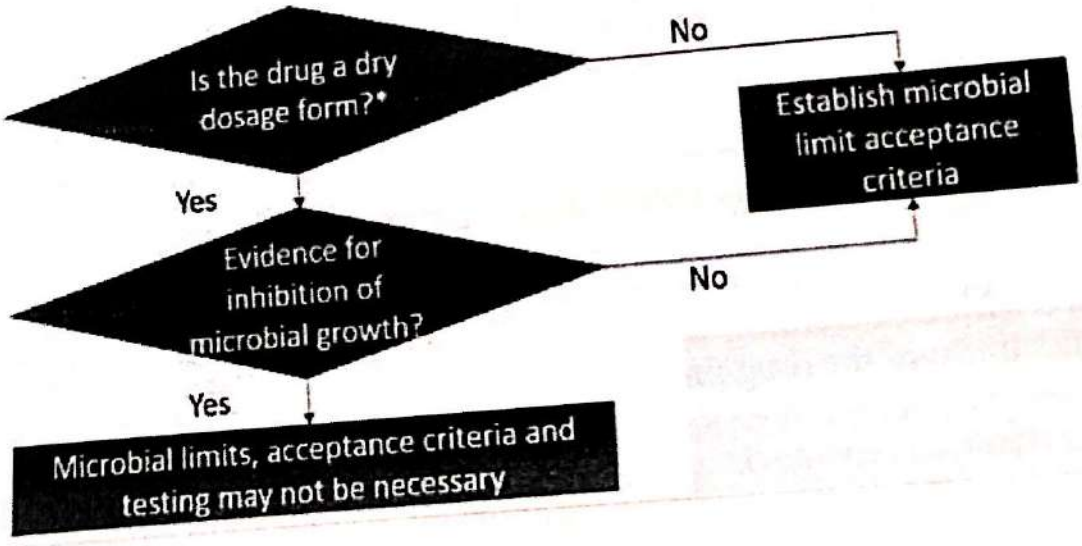
Specific tests/criteria
New drug substance

- **Microbial limits** →
- Specification the total count of aerobic microorganisms, the total count of yeasts and molds, and the absence of specific objectionable bacteria (e.g., Staphylococcus aureus, Escherichia coli, Salmonella, Pseudomonas aeruginosa) →
- These should be suitably determined using pharmacopoeial procedures.
- The type of microbial test(s) and acceptance criteria should be based on the nature of the drug substance, method of manufacture, and the intended use of the drug product.
- Sterility testing may be appropriate for drug substances manufactured as sterile and endotoxin testing may be appropriate for drug substances used to formulate an injectable drug product.
- Decision tree #6 provides additional guidance on when microbial limits should be included.

Case 1: drug contains antimicrobial activity or has



Case 2: drug has no antimicrobial agent or has no inherent antimicrobial activity



Specific tests/criteria
New drug product

- **Dissolution**:
- The specification for solid oral dosage forms normally includes a test to measure release of drug substance from the drug product.
- Single-point measurements are normally considered to be suitable for immediate-release dosage forms. For modified-release dosage forms, appropriate test conditions and sampling procedures should be established.
- For example, multiple time point sampling should be performed for extended-release dosage
- forms, and two-stage testing (using different media in succession or in parallel, as
- appropriate) may be appropriate for delayed-release dosage forms. In these cases it is important to consider the populations of individuals who will be taking the drug product (e.g.,achlorhydric elderly) when designing the tests and acceptance criteria.
- In some case dissolution testing may be replaced by **disintegration testing?!**

Dissolution

Immediate release

- It is desirable to develop test conditions when changes in dissolution rate have been demonstrated to significantly affect bioavailability .

Extended-release

- *In vitro* / *in vivo* correlation may be used to establish acceptance criteria when human bioavailability data are available for formulations exhibiting different release rates.

Specific tests/criteria
New drug product

Disintegration

- For rapidly dissolving (dissolution >80% in 15 minutes at pH 1.2, 4.0 and 6.8) products containing drugs which are highly soluble throughout the physiological range (dose/solubility volume < 250 mL from pH 1.2 to 6.8), disintegration may be substituted for dissolution.
- Disintegration testing is most appropriate when a relationship to dissolution has been established or when disintegration is shown to be more discriminating than dissolution. In such cases dissolution testing may not be necessary.
- It is expected that development information will be provided to support the robustness of the formulation and manufacturing process with respect to the selection of dissolution vs. disintegration testing.

Specific tests/criteria
New drug product